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Formula milks and later cognition: Nutrients added to enhance cognition show no benefits and may do harm

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Many claims are made for the long term importance of nutritional exposures in early life, but studies that examine the impact of such nutrition on a child's neurodevelopment often measure outcomes too prematurely for robust assessment and before full development of cognition. Thus, the linked paper by Verfürden and colleagues (doi:10.1136/BMJ-2021-065805) is impressive.¹ The researchers tracked 1763 participants in seven randomised controlled trials of novel infant formulas, started between 1993 and 2001, and linked 91% of the studies to centrally collected, objective, educational outcomes at ages 11 and 16 years.

These "dormant" trials shared similar timings and outcomes and emanated from the same research group as the new linked paper, [Author: correct?] but several differences made meta-analysis impossible; one trial began when the infants were aged 6 months, and not at birth, [Author : ok?] two studied preterm infants, one studied small for gestational age term infants, and three studied only healthy term infants. Two tested formula milks enriched with a long chain polyunsaturated fatty acid (LCPUFA), one of the many breast milk constituents with a role in brain development; one tested added iron; two tested formula milks with higher macronutrient concentrations; and two tested formulations with added sn-2 palmitate or nucleotides, not thought to relate to cognition.

None of these modified formula milks benefitted recipients' later school performance in maths or English, which was perhaps expected, as effects on early development had not been shown previously. Verfürden and colleagues' new results, however, also discount any new benefits arising later in childhood. The authors argue that the original trials were large enough to detect a true difference of at least 0.33 standard deviation (SD) scores for nationally mandated examinations in maths at age 16 years. It is, however, somewhat surprising that the original triallists believed that such limited nutritional enhancements could have had such large effects. A difference of 0.33 SD scores is nearly three times the cognitive effect of breastfeeding reported by one meta-analysis: 0.13 SD (two time points) after adjustment for maternal cognition².

An optimistic approach to the size of an expected effect in a planned trial permits a much smaller and less costly study; the numbers needed to detect a difference of 0.33 SD would be around 260 participants; to detect 0.13 SD requires 1600. This optimistic approach means that individual trials are far more likely to be under-powered to detect true effects, however, increasing the risk that the findings will be null.

A recent large systematic review of formula milk trials by Helfer et al³ found that most were funded by industry. The trials were small (median 114 participants) and even among

those published since 2015, less than half were registered in advance or had a primary outcome stated in the paper. Without trial registration, researchers can conduct many small trials and assess multiple outcomes, then publish only those that find statistically significant effects, even though these apparent effects probably occurred by chance. Helfer and colleagues' review found that 80% of studies were at high risk of bias, mainly because of selective reporting, with 92% of abstracts mentioning positive findings, despite only 42% of trials finding statistically significant differences in a stated primary outcome.

As well as exaggerating small or chance effects, small studies are less likely to detect true adverse effects. Verfürden and colleagues noted that, while none were significant, participants in five out of the seven supplemented arms fared slightly worse than controls in national maths examinations at age 16 years. Scores for both maths and English were significantly lower at age 11 years, though not at 16 years, for participants given enriched formula milk in the two LCPUFA trials. This finding is consistent with a meta-analysis by the same research group suggesting that adding LCPUFA to formula milk is harmful to cognition⁴. As Verfürden and colleagues note, despite their findings, formula milks are often supplemented with the LCPUFA docosahexaenoic acid, and in the European Union this is mandatory.⁵

Verfürden and colleagues found no differences in cognition associated with iron supplementation, but they noted that a previous study found reduced cognition at age 16 years among children who had received formula milk supplemented with iron⁶. Breast milk contains little iron, and the likely evolutionary reason for this is that iron in the gut facilitates the growth of pathogenic bacteria⁷. Manufacturers of formula milk advertise the addition of iron to follow-on milks, which could be interpreted as an advantage of formula milk over breast milk. Given the lack of benefit associated with supplementary iron⁸ and its possible adverse effect on growth⁹ and now cognition⁶, it is time to consider whether current regulations governing the composition of formula milks need review worldwide¹⁰.

Giving babies infant formula instead of breast milk has been shown convincingly and repeatedly to place babies at risk of harm¹¹. Recently published evidence suggests a need to better regulate research into infant formulas and to ensure that this evidence is used to remove unnecessary and potentially harmful nutrients from formula milk, and to prevent misleading promotional claims.

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